PATENT
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Signature

May 31, 1995
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Petra Boyle Gayle D. Wetzel Kenneth J. Lembach	REPLY BRIEF	
Serial No.:	08/026,957	Examiner:	Robert D. Budens
Filed:	March 5, 1993	Art Unit:	1806
For:	HUMAN ANTI-TNF ANTIBODIES		

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

This is a Reply Brief (three copies) responding to the Examiner's Answer mailed April 5, 1995.

The Answer withdraws rejections under 35 U.S.C. §101 and §112 (first paragraph) but contains new grounds of rejection under 35 U.S.C. §112 in view of references to Seaver, Rhein, Natanson et al. and Hill. Those references (all dated after the filing date) were newly cited by the Examiner in response to the Appellant's arguments and the use of the Declaration of Dr. Wabl.

PROVISIONAL DOUBLE PATENTING UNDER 35 U.S.C. §101: The Appellants acknowledge that the provisional double patenting rejection cannot be addressed with a Terminal Disclaimer since the claims in both the current case and patent application serial no. 08/145,060 are identical. Patent application serial no. 08/145,060 was abandoned in favor of a File Wrapper Continuation (FWC) application serial no. 08/435,246 filed May 5, 1995. The claims in the FWC may be amended and thus no longer subject this application to a double patenting rejection. Alternatively if the FWC claims are allowed in their present form this application may be abandoned. In either case, the provisional double patenting may no longer be an issue. Thus, Appellants would like to defer responding to this rejection.

REJECTIONS UNDER 35 U.S.C. §112 (first paragraph): The Examiner stated that the rejection under this statute had two parts.

UTILITY: Firstly, the Examiner indicated that there was a failure to teach utility in the application as filed. The Examiner relied on the In Re Kirk and Petrow decision (153 USPQ 49, 1967) to support that rejection. The Examiner's position appears to be that the showing of a specific binding of human anti-TNF monoclonal antibody to TNF alpha is not per se sufficient to satisfy the requirements of 35 U.S.C. §112 (for lack of utility). The Applicants disagree with this position. Unlike the situation of In Re Kirk, the Applicants here have disclosed a biological property (specific binding) which makes the claimed product inherently useful. The demonstration of specific binding of the claimed antibody makes it immediately useful as shown in the Wabl Declaration.

It is the Applicant's position that a mere demonstration of binding of a new antibody to a given antigen demonstrates a biological activity which is sufficient to satisfy the requirements of 35 U.S.C. §112 (first paragraph). It is respectfully submitted that the Examiner's reliance on Brenner v. Manson (148 USPQ 689, 1966) is misplaced since the Applicants have made a showing that their claimed human antibody does in fact specifically bind to TNF alpha. It is submitted that the current guidelines for utility in biotechnology cases are more suitably addressed in a recently issued decision In Re Brana, 34 USPQ 2d, 1436-1444, 1995.

ENABLEMENT: The Examiner's second objection under 35 U.S.C. §112 (first paragraph) appears to be that the Applicants have not provided enough information to enable the scope of the claims.

THE SEAVER REFERENCE: The Examiner has cited Seaver to show that developing a monoclonal antibody suitable for diagnostics is not a trivial matter. In response to this the Applicants would like to point out that the claims themselves are not concerned with a diagnostic use of the antibodies. The Wabl Declaration refers to potential diagnostic use (among other uses) of the antibodies. Dr. Wabl also indicated that such usefulness might have application in purification purposes as well as other uses. Very importantly, the Wabl Declaration shows that anti-TNF antibodies (non-human) are currently being sold. It is respectfully submitted that the sales of other (non-human) antibodies that bind to TNF is overwhelming evidence that such antibodies are useful.

The Examiner also criticized the Appellant's use of the first Wabl Declaration (to show enablement) since the Declaration refers to both the application itself and a published article by the Applicants in Cellular Immunology, 152, 569-581 (1993). Enclosed herewith is a second subsequently dated Declaration from Dr. Wabl in which he indicates that the patent application itself is sufficient to satisfy the enablement requirements of the patent statue. It should be noted that this second Declaration of Dr. Wabl has also been submitted in the Continuation-In-Part case and the recently filed File Wrapper Continuation application.

THE RHEIN REFERENCE: The Examiner relied on Rhein (describing other anti-TNF antibodies) to show that some clinical studies involving the use of anti-TNF agents including monoclonal antibodies have failed. However, the alleged failure of other antibodies was in reference to FDA standards of efficacy which are different from the standards of utility under the patent statute. The claimed antibodies are, unlike those of Rhein, human antibodies. Further, it is the Appellant's position that the In Re Brana decision makes the use of the FDA standards of Rhein inappropriate as there is no patent law requirement that the claimed antibodies must be supported with human clinical data.

THE NATANSON ET AL. REFERENCE: Likewise, the Examiner cited Natanson et al. to indicate that anti-TNF therapies have been beneficial in some animals but clearly did not improve survival in initial human trials. The Examiner noted that the authors point out that in one anti-TNF therapy there was actual evidence of harm. It is submitted that even evidence of harm is not a bar to patentability. For example, it is known that many compounds can be harmful under certain conditions. Yet those compounds can still be patentable as long as other requirements are met.

Again, it is respectfully submitted that there are no claims being made in this application to clinical utility. The claims are directed to defined antibodies. It appears to be the Examiner's presumption that these antibodies may be used for clinical applications that is driving the rationale for the rejection and, it is respectfully submitted, such presumption is not permitted under the patent law.

THE HILL REFERENCE: Lastly, the Examiner cited Hill to teach that if an association constant for antibody and antigen is too high, it may be difficult to recover the antigen in the antibody. Apparently this reference was cited to minimize the Applicant's argument that any new antibody could always be used for purification. Again, it is respectfully submitted that this reference is improperly cited as it is not the function of the patent application to provide immediately the best possible antibody to attain a certain goal. It is only enough to demonstrate, as in this case, that the claimed antibody is new, useful and non-obvious and that specific binding has occurred. From that, one skilled in the art could readily accept the antibody as is or optimize the use of the antibody to attain whatever properties might be deemed appropriate, depending on the use.

The Examiner appears to have taken the position that under 35 U.S.C. §112 the Applicants have not provided enough information to enable the scope of claimed invention. At page 13 in the Answer the Examiner indicated that the Applicants appear to rely on "providence" for obtaining desired antibodies. It is the Appellant's position that, given the Applicants' discovery that it is in fact possible to make human antibodies that bind specifically to TNF alpha, one skilled in the art can now readily duplicate this work and generate other human anti-TNF antibodies. The Applicants themselves have demonstrated this with several examples producing antibodies of both the IgM and the IgG isotopes. See Table I at page 13. See also the enclosed Wabl Declaration dated January 24, 1995.

USE OF CMV DONORS: Lastly, the Examiner's comment that the production of the claimed antibodies may require a CMV positive donor for the lymphocytes is not understood. All claims are concerned with a human monoclonal antibody that bind specifically to TNF alpha. The claims are not limited by the source of lymphocytes from which the human antibodies are made. In the Declaration submitted by Dr. Wetzel, he explained in detail why CMV positive donors were not necessarily essential to produce the claimed antibodies. In any case, there are no methods of making claims or product-by-process claims in this application. Therefore, the Applicants do not understand the Examiner's position that CMV positive donors might be needed to make the claimed antibodies. Product claims by definition are not limited to a particular process of manufacture.

The above comments address the new issues raised by the Examiner in the Answer. In view of the above comments and the enclosed second Declaration of Dr. Wabl, it is respectfully submitted that the claims in this Application define patentable subject matter and that they should have been allowed by the Examiner.

Respectfully submitted,

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Date

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